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GABAergic Abnormalities Occur in Experimental Models of Focal and Genetic Epilepsy

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Two types of experimental models of epilepsy were studied with morphological methods. The first type resembles post-traumatic focal epilepsy and can be generated by alumina gel implants into the sensorimotor cortex of monkeys. The epileptic focus in these monkeys displays a preferential loss of cortical GABAergic neurons and axon terminals. Recent studies indicate that this loss occurs following the alumina gel treatments and prior to the onset of clinical seizures. These findings add further support to the hypothesis that a loss of GABAergic inhibition plays a causal role in focal epilepsy. Two genetic models of epilepsy were analyzed with biochemical and immunocytochemical methods for GABAergic neurons and synapses. The seizure-sensitive gerbil and the genetically epilepsy-prone rat display an increase in the number of GABAergic neurons and terminals in specific brain regions that also show significant increases in the biochemical level of GABA as compared to non-epileptic animals of the same species. These brain regions are essential for seizure activity because lesions in these areas block seizures. Furthermore, it appears that these brain regions are involved in the analysis of the stimuli that generate seizures. One possible hypothesis to explain seizures in these genetic models is increased disinhibition of excitatory projection neurons in the affected brain regions. These findings suggest that GABAergic abnormalities occur in experimental models of both focal and genetic epilepsy and provide further support for the use of antiepileptic drugs that act at the GABA receptor.

The understanding of human epilepsy is a goal that neuroscientists have endeavored to reach over the past century. Numerous approaches have been used to analyze the basic mechanisms of human epilepsy, including an analysis of experimental models that resemble its many varieties (see Delgado-Escueta, Ward, Woodbury, and Porter, 1986). The use of animal models has aided in our understanding of epilepsy. For example, the ability to record in a hippocampal slice preparation the electrophysiology of neurons that display high activity in an epileptic focus has provided important insights as to how neurons must synchronize their activity for bursting (Dudek, Snow, and Taylor, 1986; Dudek

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and Christian, this issue, 1987). Also, the use of genetic models has provided new data on the mode of inheritance of epilepsy (Noebels, 1986; Seyfried, Glaser, Yu, and Palayoor, 1986). Other studies that use anatomical methods have shown the importance of GABAergic neurons for the normal maintenance of inhibitory function in the cortex (Houser, Harris, and Vaughn, 1986; Ribak, 1985; Ribak, Bradburne, and Harris, 1982; Ribak, Harris, Vaughn, and Roberts, 1979; Ribak, Hunt, Bakay, and Oertel, 1986; Ribak, Joubran, and Bakay, 1987). Finally, these epileptic models have been helpful in the development of new antiepileptic drugs that appear to act principally at a GABA-benzodiazepine-barbiturate receptor complex (Olsen, Wamsley, Lee, and Lomax, 1986).

These studies of the basic mechanisms of the epilepsies have demonstrated a number of factors that are involved with the initiation of seizures (Delgado-Escueta et al., 1986). They include a role for GABA, glutamate, $Na^{+}K$ pump, Ca^{2+} influx, catecholamines, acetylcholine, Ca^{2+} calmodulin protein kinase and membrane lipid matrix. The studies from my laboratory have used anatomical methods to explore the role of GABA in experimental models of focal and genetic epilepsy.

The early work that showed a morphological change in the number of GABA neurons in focal epilepsy started in the mid seventies when I was working at the City of Hope Medical Center with Dr. Eugene Roberts. One of the major stimuli for this work came from a paper written by Meldrum (1975) that had reviewed pharmacological and biochemical data that demonstrated a role of GABA inhibition in epilepsy. Thus, a number of drugs were known to antagonize GABA receptors and these caused seizures. In contrast, other drugs that were GABA agonists ameliorated seizures. These findings have been used to design new therapeutic drugs for the treatment of epilepsy (Olsen, 1981).

The experimental model of focal epilepsy that we used initially for these studies was the alumina gel treated monkeys. Briefly, the central sulcus of the monkey is injected with alumina gel to form a granuloma. In contrast, the contralateral central sulcus is not injected and the cortex around this latter site serves as a control. Following two to three months, these so-called chronic animals develop seizure activity that is centered around the focus where the alumina gel cream was injected and where a significant loss of GABAergic somata and axon terminals occurs (Ribak et al., 1986). The contralateral cortex does not display epileptic activity. It is interesting to note that when the alumina gel granuloma is excised from these epileptic monkeys, the seizures stop (Harris and Lockard, 1981).

Subsequent to these studies, an analysis of other models of epilepsy was made to determine whether the same GABA defect could be found. Two models of genetic epilepsy were examined and they displayed paradoxical increases in the number of GABAergic neurons in specific brain regions that could be involved in the analysis of the stimuli that cause seizures (Peterson and Ribak, 1987;

Peterson, Ribak, and Oertel, 1985; Roberts, Ribak, and Oertel, 1985). These models included the seizure-sensitive gerbil and the genetically epilepsy-prone rat (GEPR). The results of these studies will be presented to illustrate how the GABAergic system can display different abnormalities in animal models of epilepsy.

Results and Discussion

Initially, the morphological studies utilized an antiserum to glutamate decarboxylase (GAD), the synthesizing enzyme for GABA, that was developed and characterized at the City of Hope (see Roberts, 1986; Roberts, this issue, 1987). The methods used to demonstrate the immunocytochemical localization of GABAergic axon terminals in these preparations have been previously described (Ribak, 1978; Ribak et al., 1979). The more recent studies used a GAD antiserum that was raised in sheep (Oertel, Schmechel, Mugnaini, Tappaz, and Kopin, 1981).

Focal Epilepsy

The first immunocytochemical study of the alumina gel model of focal epilepsy (Ribak et al., 1979) showed that the staining for GABAergic axon terminals was significantly decreased at the epileptic focus, as well as at a site about 1 cm from the focus which is referred to as the parafocus. The normal cortex showed the typical pattern of immunostaining for GAD-containing axon terminals with many terminals apposed to the surfaces of pyramidal cell bodies, basal dendrites and axon initial segments (see Figure 1). These terminals are derived from stellate cells or non-pyramidal neurons found in the same or adjacent cortical layers. In contrast, the number of GAD-containing axon terminals at the actual epileptic focus is reduced significantly around the cell bodies and axon initial segments. This light microscopic finding was corroborated in two subsequent electron microscopic studies that showed significant losses (80% or more) of axon terminals that formed symmetric synapses with the somata and axon initial segments of pyramidal cells (Ribak, 1985; Ribak, Bradburne, and Harris, 1982).

These electron microscopic findings provided important data on two well-characterized GABAergic neurons of the cerebral cortex, the basket and chandelier cells. The basket cell has an axonal plexus that forms pericellular nests around pyramidal cells in layer V (see Jones, 1981; Jones, this issue, 1987). The terminals from this plexus form symmetric, axosomatic synapses (see Figure 2), and virtually all of the terminals that contact the somata of pyramidal cells are of this type (Peters and Fairén, 1978). Therefore, an examination of routine electron microscopic preparations allowed for an assessment of the basket plexus. The quantitative analysis of these axosomatic

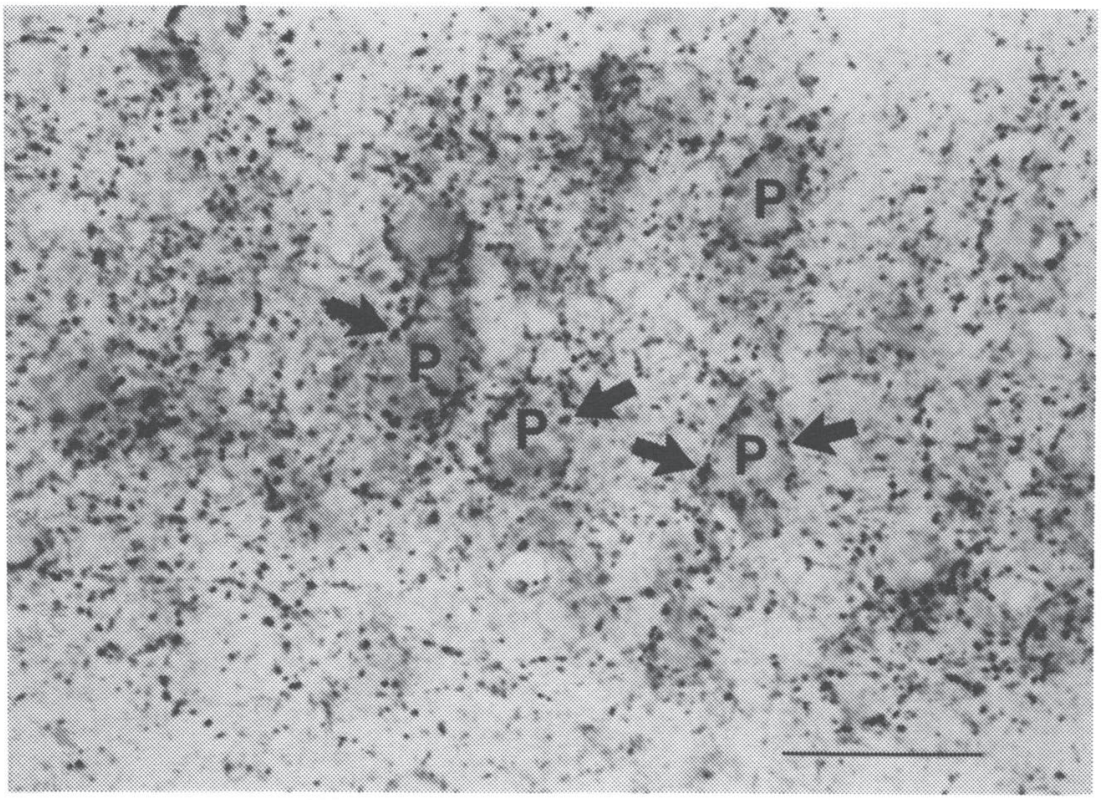

Figure 1: Light photomicrograph of GAD-immunoreactive axon terminals (arrows) that form a pericellular basket plexus with pyramidal cell bodies (P) in the motor cortex. Seizure-sensitive gerbil. Scale bar = 50 μm.

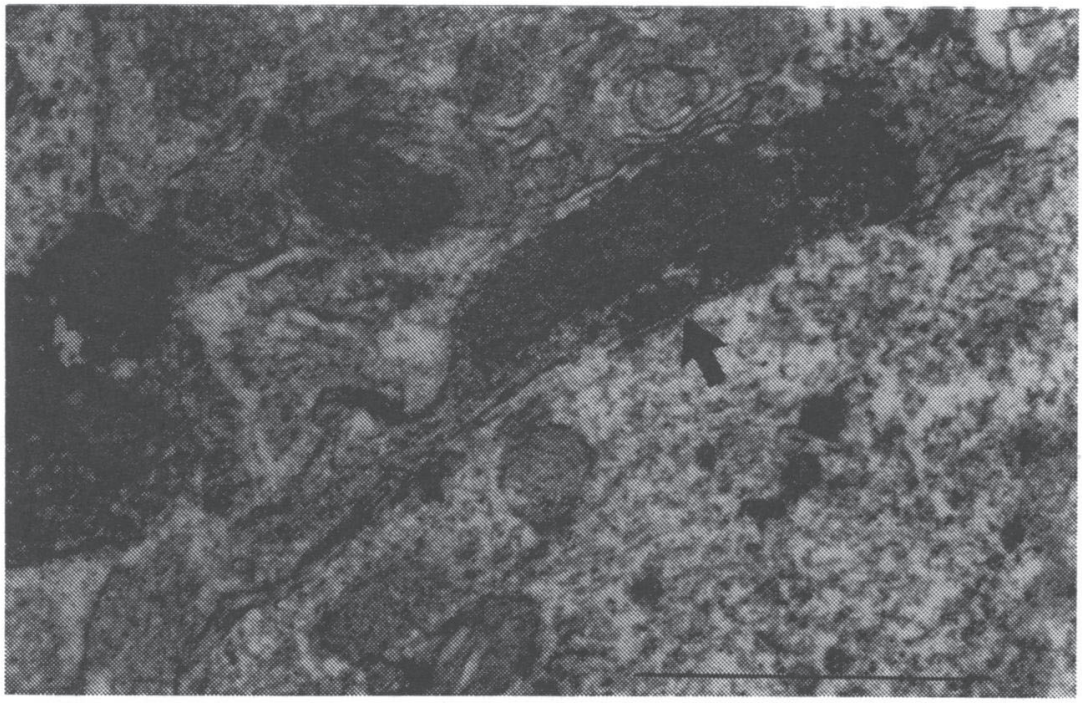

Figure 2: Electron micrograph of a GAD-immunoreactive axon terminal that forms a symmetric axosomatic synapse (arrow). Inferior colliculus. Scale bar = 1 μm.

synapses showed that they were reduced by 80% at the epileptic focus as compared to the contralateral non-epileptic cortex (Ribak et al., 1982). Glial processes that were apposed to the somal surface had increased their apposition by 100% (Ribak et al., 1982), and this finding suggested that many GABAergic axon terminals had degenerated. Since GABA has a strong inhibitory effect on cortical neurons (see Krnjević, this issue, 1987, the loss of such a significant number of GABAergic basket cell axons at the epileptic focus probably causes the layer V pyramidal cells to be more hyperexcitable than normal.

A subsequent electron microscopic study (Ribak, 1985) showed that the chandelier cell, another cortical GABAergic cell type, had a reduced function at epileptic foci because its axonal plexus had virtually degenerated. The chandelier cell is described to have a small soma in layers II and III and an axon that forms a number of vertical tapers with the surrounding axon initial segments of pyramidal cells from these same two layers (DeFelipe, Hendry, Jones, and Schmechel, 1985; Fairén and Valverde, 1980; Peters, Proskauer, and Ribak, 1982; Somogyi, Freund, and Cowey, 1982). The terminals at this site form only symmetric synapses (see Figure 3A), and virtually all of them were shown to contain immunoreactivity for GAD (DeFelipe et al., 1985; Peters et al., 1982). Axon terminals of chandelier cells were identified in the cerebral cortex of monkeys with alumina gel treatments. The initial segments of pyramidal cells in non-epileptic cortex showed a normal number of axons that formed symmetric, initial segment synapses (Figure 3A). In contrast, the axon initial segments of pyramidal neurons in epileptic cortex were mainly apposed by glial processes (see Figure 3B). Therefore, the large loss of these axons in epileptic foci (Ribak, 1985) may also contribute to the hyperexcitability of neurons in this region.

More recently, we have completed two studies using a different anti-GAD serum than the one used in the initial analysis (Ribak et al., 1979) because this latter antiserum stains GAD-containing cell bodies without the use of colchicine (Oertel et al., 1981). These studies have shown that the number of GABAergic cell bodies is significantly decreased at epileptic foci as compared to the contralateral non-epileptic cortex (Ribak et al., 1986; Ribak, Joubran, and Bakay, 1987). In these studies, monkeys were sacrificed both prior to seizure activity (preseizing) and following long seizure activity (chronic). The results from the preseizing monkeys showed a significant loss (about 25%) of GABA neurons in the focus. In the chronic monkeys that had seizures on-going for at least a month or two, the results showed that both the foci and parafoci in these animals had a significant loss of GABAergic neurons as compared to the non-epileptic contralateral cortex. These data indicate that GABA neurons are lost prior to seizure activity and that the loss of GABA neurons increases in magnitude as the length of duration of seizures increases. The loss of GABA neurons in preseizing monkeys is consistent with the reported significant loss of

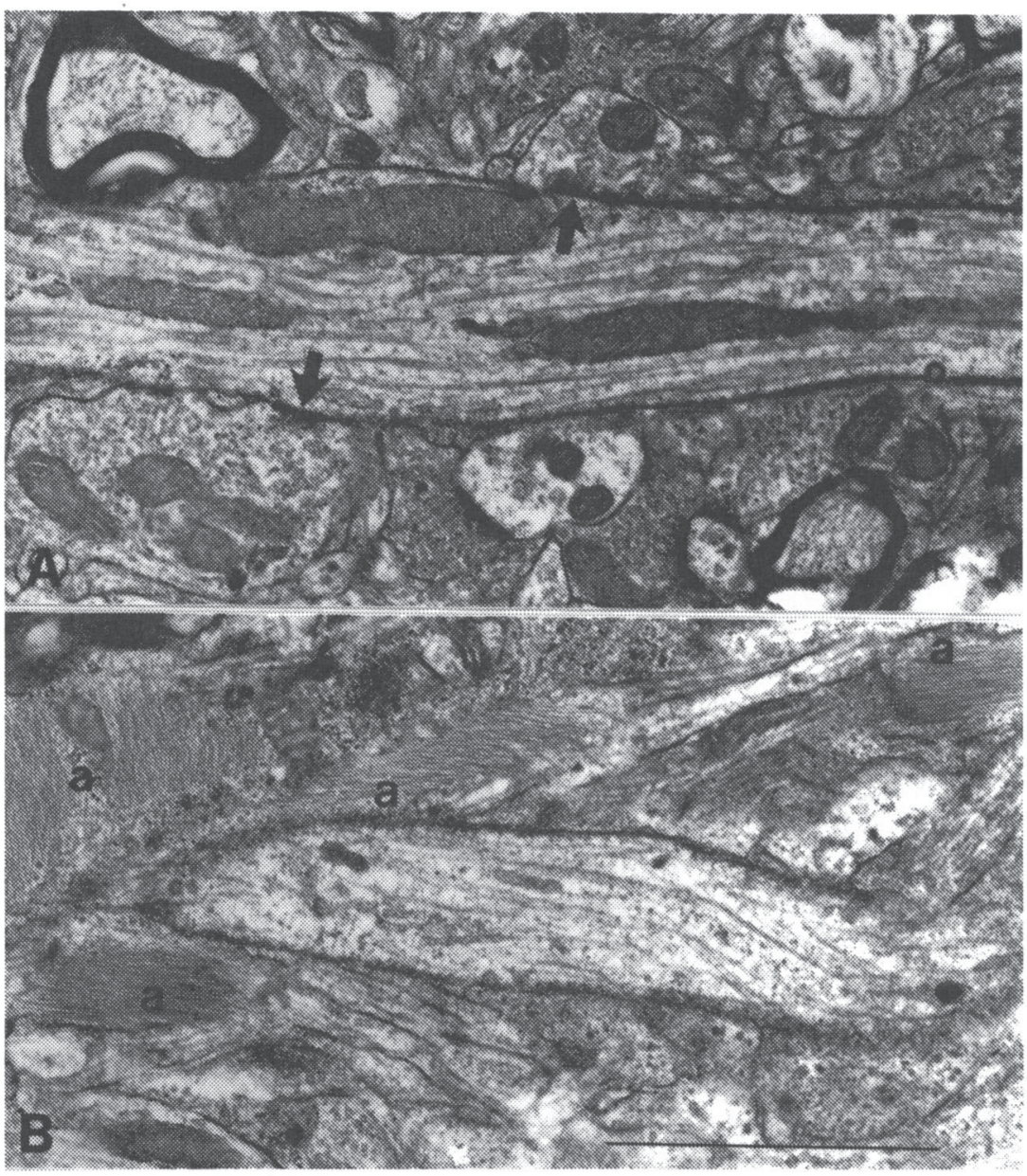

Figure 3: Electron micrographs of axon initial segments of pyramidal cells in layer III of monkey sensorimotor cortex. A shows two axon terminals that form initial segment synapses (arrows) from non-epileptic cortex. B shows an initial segment from an alumina gel epileptic focus. Note the numerous reactive astrocytic processes (a) that are found adjacent to it. Scale bar = 1 μm.

GABAergic axon terminals in preseizing monkeys (Houser, Harris, and Vaughn, 1986). Together, these results (see Table 1) indicate that the loss of GABA neurons and axon terminals plays a causal role in the initiation of seizures in the alumina gel model of focal epilepsy. These data provide the first morphological evidence that GABAergic neurons are lost at epileptic foci and the resulting release from inhibition may cause the hyperexcitability of neurons at the epileptic focus.

How has the loss of GABA neurons affected the cortical circuitry? In the epileptic cortex, a large number of basket and chandelier cells are lost that

normally give rise to a feedback inhibition of excitatory pyramidal neurons in the cerebral cortex. When they are absent, a recurrent excitatory circuitry could characterize the neurons in the epileptic focus and provide a basis for the epileptic activity. Thus, a loss of inhibition is the hallmark of the focal epilepsy model. This conclusion from the anatomical studies is consistent with the results from biochemical studies performed on tissue obtained from monkeys treated with alumina gel (Bakay and Harris, 1981) and humans with tumors (Lloyd, Bossi, Morselli, Munari, Rogier, and Loiseau, 1986).

Table 1

Percentage Loss of Somata and Terminals at Alumina Gel Epileptic Foci

Study	GABAergic Terminal Loss		GABAergic Somata Loss	
	Pre	Chronic	Pre	Chronic
Ribak et al., 1979	—	58–62%	—	—
Houser et al., 1986	14–22%	24–33%	—	—
Ribak et. al., 1986	—	—	—	35–52%
Ribak, Joubran, and Bakay, 1987	—	—	23–44%	42–61%

Why are the GABAergic neurons lost at epileptic foci caused by alumina gel in monkeys and at epileptic foci caused by tumors in humans? Alumina gel and tumor cells must play a role in damaging GABAergic neurons because surgical control tissue failed to display a significant loss of GABAergic neurons (Ribak et al., 1986; Ribak, Joubran, and Bakay, 1987). It is possible that these regions of cortex become ischemic and this ischemia leads to the loss of GABAergic neurons because terminals with features similar to GABAergic terminals are lost in young postnatal monkeys exposed to hypoxic conditions (Sloper, Johnson, and Powell, 1980). Since physiological data indicate that GABAergic local circuit neurons are more active than pyramidal neurons (Schwartzkroin, 1986), the GABAergic neurons would be more susceptible to ischemia because they would have a higher demand for oxygen and nutrients. Consistent with this notion is the finding that terminals apposed to somata and initial segments that probably arise from basket and chandelier cells, respectively display more mitochondria per terminal than other terminals in the cortex (Ribak 1985; Ribak et al., 1982), and this finding may relate to the higher cellular activity of these two types of GABA neuron. Nevertheless, the reported loss of such inhibitory terminals that are strategically located near the site of spike initiation may lead to hyperexcitability of the pyramidal neurons.

Genetic Epilepsy

To determine whether other models of epilepsy display the same type of GABAergic defect observed in the monkey model of focal epilepsy, two genetic

models were examined: the seizure-sensitive gerbil and the genetically epilepsy prone rat (GEPR). The hippocampal dentate gyrus of the seizure-resistant gerbil displays GAD-positive basket cells subjacent to the granule cell layer. We reported an increase in the number of these GABAergic basket cells in the seizure-sensitive gerbil, and this increase was most substantial in the septal or dorsal portion (Peterson and Ribak, 1987; Peterson et al., 1985). Other brain regions such as the motor cortex (Figure 1), thalamic reticular nucleus and substantia nigra displayed normal numbers of GABAergic somata (Peterson and Ribak, 1987). In addition to the increased number of GABAergic somata in the dentate gyrus, the intensity of staining of the terminals in the granule cell layer appeared to be enhanced. These results were confirmed in a recent biochemical study that showed a significant increase in the level of GAD activity in the whole hippocampus of young gerbils with medium seizure-sensitivity (Löscher, 1987). However, older gerbils with high seizure-sensitivity did not display an increase and this discrepancy may be explained by the use of the whole hippocampus for biochemical analysis rather than only the septal third.

Another morphological difference between these two strains of gerbils was observed in electron microscopic preparations (Peterson et al., 1985). The granule cell axons that are referred to as mossy fibers display normal features in the seizure-resistant animals. For example, they have large numbers of round synaptic vesicles and form typical asymmetric synaptic contacts with dendritic spines. In contrast, the seizure-sensitive gerbils displayed mossy fibers that were depleted of most of their synaptic vesicles, especially in areas of the terminal adjacent to the active zones. This type of axonal morphology is similar to that found in another model of epilepsy where GABA antagonists caused changes in mossy fibers (Nitsch and Rinne, 1981).

These two sets of findings seemed to contradict each other because an increase in the number of GABAergic neurons associated with granule cells should not cause changes in the morphology of granule cell axons that are similar to those found in seizure activity. One possible explanation for these paradoxical findings was that the GABA receptors were not normal in the granule cell layer. Recently, Olsen et al. (1986) have examined the distribution of benzodiazepine receptors in gerbils and have reported no differences in their number in the dentate gyrus. However, there was a 30% decrease in the number of these receptors in the substantia nigra of seizure-sensitive gerbils. An alternative explanation for the changes in the hippocampus was the possibility that the basket cells found in the seizure-resistant animals might have a normal number of GABAergic axon terminals found apposed to their cell bodies, but the basket cells in seizure-sensitive animals might have more of these axon terminals. Preliminary light and electron microscopic data support this alternative that would suggest an increase of disinhibition in the dentate gyrus of seizure-sensitive gerbils (Peterson and Ribak, 1985).

To determine whether the afferents to the hippocampus are essential for epileptic activity in seizure-sensitive gerbils, knife cuts of the perforant path fibers were made and the surviving gerbils were tested for seizure activity (Ribak and Khan, 1987). The results of this study indicated that bilateral lesions of this type prevent seizures from occurring. In contrast, bilateral lesions of the fornix had no effect on seizure activity (see Table 2). This study provides further evidence for a hippocampal role in the generation and/or propagation of seizures in this model of epilepsy.

Table 2

Effects of Knife Cuts of Hippocampal Pathways on Seizure Behavior in Seizure-Sensitive Gerbils

Site of Cuts	Gerbil #	Seizure Score	
		Before Surgery	After Surgery
Bilateral fornix & perforant path	80	4.8	0
	28	2.7	0
	68	2.0	0
Bilateral perforant path	56	4.1	0
	55	3.5	0
	49	2.1	0
	58	1.9	0
	82	1.0	0
Bilateral fornix	52	3.1	3.8
	50	1.6	0
	67	1.2	3.4
	90	1.0	3.3
Unilateral perforant path	77	1.6	2.3
	92	3.8	4.3
Sham-operated	50a	4.6	4.75
	66	1.5	1.75

A working hypothesis for this model of epilepsy involves a circuitry of increased disinhibition where GABAergic basket cells contact other basket cells to inhibit them from inhibiting granule cells of the hippocampal dentate gyrus. Physiological studies are required to demonstrate this type of circuitry.

The genetically epilepsy prone rat (GEPR) exhibits severe generalized seizures in response to intense auditory stimuli (Jobe, Picchioni, and Chin, 1973). Previous lesion studies have shown that the primary neuronal pathways involved in the manifestation of audiogenic seizures are subcortical because partial or total ablation of cortex does not prevent seizures whereas bilateral lesions of the inferior colliculus (IC) and brainstem reticular formation block seizure activity (Browning, Nelson, Mogharreban, Jobe, and Laird, 1985; Kesner, 1966; Koenig, 1958). Other data have shown that the IC is abnormal in the

GEPR. An increase in after discharge-like responses similar to that observed in other types of seizures has been observed in the IC of GEPR (Faingold, Gehlbach, Travis, and Caspary, 1986). Also, neurons in the IC of GEPR are less sensitive to GABA and benzodiazepine iontophoresis than neurons in the IC of control rats (Faingold, Gehlbach, and Caspary, 1986).

The IC of the GEPR was analyzed with GAD immunocytochemical methods and it displayed a significant increase in the number of GABAergic neurons (Roberts, Ribak, and Oertel, 1985). This increase was more prominent in the center of the rostrocaudal extent of the IC where a 200% increase in the number of small cells occurred and a 90% increase in the number of medium-sized cells was also found. To determine whether more total neurons were present in the IC of GEPR, Nissl-stained sections were analyzed and they showed increases in the number of both small and medium-sized cells in the GEPR (Roberts, Ribak, and Oertel, 1985). A subsequent study showed that the increase in the total number of neurons occurs in the young offspring of GEPRs prior to the onset of seizure activity (Roberts, Kim, and Ribak, 1985). These latter data indicate that the increase in the number of GABAergic and total neurons in the IC is not compensatory for the seizure activity, but instead may be a determinant of seizure behavior.

Previous biochemical studies have shown that a small (10 to 35%), insignificant increase in GABA occurs in the IC of GEPRs (Chapman, Faingold, Hart, Bowker, and Meldrum, 1986; Huxtable, Laird, Bonhaus, and Thies, 1982). Since the largest increase in the number of GABA neurons occurred in the central nucleus of the IC with much smaller increases in the other regions of the IC (Roberts, Ribak, and Oertel, 1985), it was possible that the change in the central nucleus was masked by the inclusion of these other nuclei of the IC in the previous biochemical studies. Recently, GABA was measured selectively for the central nucleus of the IC and a 2.3 fold significant increase in the level of GABA was reported (Ribak, Byun, Ruiz, and Reiffenstein, 1987). Other regions of the brain that were analyzed did not show any changes in the levels of GABA (see Table 3). The magnitude of the increase in the level of GABA in the central nucleus of the IC of the GEPR as compared

Table 3

GABA LEVELS (μmol/g $\pm$ SE)

Brain Region	Non-epileptic Rats	Genetically Epilepsy Prone Rats
Central nucleus of inferior colliculus	0.314 $\pm$ 0.061	0.721 $\pm$ 0.073
Cerebellum	2.104 $\pm$ 0.290	1.536 $\pm$ 0.346
Occipital cortex	2.702 $\pm$ 0.403	1.751 $\pm$ 0.151
Temporal cortex	2.127 $\pm$ 0.297	2.078 $\pm$ 0.319
Sensorimotor cortex	2.132 $\pm$ 0.221	2.009 $\pm$ 0.421

to that of non-epileptic Sprague-Dawley rats is consistent with the 3.0 fold increase in the number of GABAergic neurons observed in this region.

These data support the notion that an abnormal or dysfunctional GABAergic system exists in the IC of GEPRs. This abnormality could involve increased disinhibition of excitatory projection neurons during intense auditory stimuli or it could involve a problem with the $GABA_a$ receptor. Further studies are required to resolve why high GABA and low efficacy occur in the IC.

References

Bakay, R. A. E., and Harris, A. B. (1981). Neurotransmitter, receptor and biochemical changes in monkey cortical epileptic foci. *Brain Research*, *296*, 387–404.

Browning, R. A., Nelson, D. K., Mogharreban, N., Jobe, P. C., and Laird, H. E. II. (1985). Effect of midbrain and pontine tegmental lesions on audiogenic seizures in genetically epilepsy-prone rats. *Epilepsia*, *26*, 175–183.

Chapman, A. G., Faingold, C. L., Hart, G. P., Bowker, H. M., and Meldrum, B. S. (1986). Brain regional amino acid levels in seizure susceptible rats: Changes related to sound-induced seizures. *Neurochemistry International*, *8*, 273–279.

DeFelipe, J., Hendry, S. H. C., Jones, E. G., and Schmechel, D. (1985). Variability in the terminations of GABAergic chandelier cell axons on initial segments of pyramidal cell axons in the monkey sensory-motor cortex. *Journal of Comparative Neurology*, *231*, 364–384.

Delgado-Escueta, A. V., Ward, A. A., Woodbury, D. M., and Porter, R. J. (1986). *Basic mechanisms of the epilepsies. Molecular and cellular approaches*. New York: Raven Press.

Dudek, F. E., and Christian, E. P. (1987). Inhibition, local excitatory interactions and synchronization of epileptiform activity in hippocampal slices. *Journal of Mind and Behavior*, *8*, 619–634.

Dudek, F. E., Snow, R. W., and Taylor, C. P. (1986). Role of electrical interactions in synchronization of epileptiform bursts. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 593–618). New York: Raven Press.

Fairén, A., and Valverde, F. (1980). A specialized type of neuron in the visual cortex of cat. A Golgi and electron microscopic study of chandelier cells. *Journal of Comparative Neurology*, *194*, 761–779.

Faingold, C. L., Gehlbach, G., and Caspary, D. M. (1986). Decreased effectiveness of GABA-mediated inhibition in the inferior colliculus of the genetically epilepsy-prone rat. *Experimental Neurology*, *93*, 145–159.

Faingold, C. L., Gehlbach, G., Travis, M. A., and Caspary, D. M. (1986). Inferior colliculus neuronal response abnormalities in genetically epilepsy prone rats: Evidence for a deficit of inhibition. *Life Sciences*, *39*, 869–878.

Harris, A. B., and Lockard, J. S. (1981). Absence of seizures or mirror foci in experimental epilepsy after excision of alumina and astrogliotic scar. *Epilepsia*, *22*, 107–122.

Houser, C. R., Harris, A. B., and Vaughn, J. E. (1986). Time course of the reduction of GABA terminals in a model of focal epilepsy: A glutamic acid decarboxylase immunocytochemical study. *Brain Research*, *383*, 129–145.

Huxtable, R. J., Laird, H. E., Bonhaus, D., and Thies, A. C. (1982). Correlations between amino acid concentrations in brains of seizure susceptible and seizure resistant rats. *Neurochemistry International*, *4*, 73–78.

Jobe, P. C., Picchioni, A. L., and Chin, L. (1973). Role of brain norepinephrine in audiogenic seizure in the rat. *Journal of Pharmacology and Experimental Therapeutics*, *184*, 1–10.

Jones, E. G. (1981). Anatomy of cerebral cortex: Columnar input-output organization. In F. O. Schmitt, F. G. Worden, G. Adelman, and S. G. Dennis (Eds.), *The organization of the cerebral cortex* (pp. 199–235). Cambridge: MIT Press.

Jones, E. G. (1987). GABA-peptide neurons of the primate cerebral cortex. *Journal of Mind and Behavior, 8*, 519–536.

Kesner, R. P. (1966). Subcortical mechanisms of audiogenic seizures in the rat. *Experimental Neurology, 15*, 192–205.

Koenig, E. (1958). The effects of auditory pathway interruption on the incidence of sound induced seizures in rats. *Journal of Comparative Neurology, 108*, 383–392.

Krnjević, K. (1987). GABAergic inhibition in the neocortex. *Journal of Mind and Behavior, 8*, 537–548.

Lloyd, K. G., Bossi, L., Morselli, P. L., Munari, C., Rogier, M., and Loiseau, H. (1986). Alterations of GABA-mediated synaptic transmission in human epilepsy. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 1033–1044). New York: Raven Press.

Löscher, W. (1987). Hippocampal glutamate decarboxylase activity is not altered in gerbils with high seizure susceptibility. *Biochemical Pharmacology, 36*, 979–982.

Meldrum, B. S. (1975). Epilepsy and GABA-mediated inhibition. *International Review of Neurobiology, 17*, 1–36.

Nitsch, C., and Rinne, U. (1981). Large dense-core vesicle exocytosis and membrane recycling in the mossy fibre synapses of the rabbit hippocampus during epileptiform seizures. *Journal of Neurocytology, 10*, 221–219.

Noebels, J. L. (1986). Mutational analysis of inherited epilepsies. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 97–113). New York: Raven Press.

Oertel, W. H., Schmechel, D. E., Mugnaini, E., Tappaz, M. L., and Kopin, I. J. (1981). Immunocytochemical localization of glutamate decarboxylase in rat cerebellum with a new antiserum. *Neuroscience, 6*, 2715–2735.

Olsen, R. W. (1981). The GABA postsynaptic receptor-ionophore complex: Site of action of convulsant and anticonvulsant drugs. *Molecular and Cellular Biochemistry, 39*, 261–279.

Olsen, R. W., Wamsley, J. K., Lee, R. J., and Lomax, P. (1986). Benzodiazepine/barbiturate/GABA receptor-chloride ionophore complex in a genetic model for generalized epilepsy. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 365–378) New York: Raven Press.

Peters, A., and Fairén, A. (1978). Smooth and sparsely spined stellate cells in the visual cortex of the rat: A study using a combined Golgi-electron microscope technique. *Journal of Comparative Neurology, 181*, 129–172.

Peters, A., Proskauer, C. C., and Ribak, C. E. (1982). Chandelier cells in rat visual cortex. *Journal of Comparative Neurology, 206*, 397–416.

Peterson, G. M., and Ribak, C. E. (1985). Morphological evidence for increased inhibition of basket cells in the dentate gyrus of Mongolian gerbils. *Society for Neuroscience Abstracts, 11*, 1321.

Peterson, G. M., and Ribak, C. E. (1987). Hippocampus of the seizure-sensitive gerbil is a specific site for anatomical changes in the GABAergic system. *Journal of Comparative Neurology, 261*, 405–422.

Peterson, G. M., Ribak, C. E., and Oertel, W. H. (1985). A regional increase in the number of hippocampal GABAergic neurons and terminals in the seizure sensitive gerbil. *Brain Research, 340*, 384–389.

Ribak, C. E. (1978). Aspinous and sparsely-spinous stellate neurons in the visual cortex of rats contain glutamic acid decarboxylase. *Journal of Neurocytology, 7*, 461–478.

Ribak, C. E. (1985). Axon terminals of GABAergic chandelier cells are lost at epileptic foci. *Brain Research, 326*, 251–260.

Ribak, C. E., Bradburne, R. M., and Harris, A. B. (1982). A preferential loss of GABAergic, inhibitory synapses in epileptic foci: A quantitative ultrastructural analysis of monkey neocortex. *Journal of Neuroscience, 2*, 1725–1735.

Ribak, C. E., Byun, M. Y., Ruiz, G. T., and Reiffenstein, R. J. (1987). Increased levels of amino acid neurotransmitters in the inferior colliculus of the genetically epilepsy-prone rat. *Epilepsy Research* (in press).

Ribak, C. E., Harris, A. B., Vaughn, J. E., and Roberts, E. (1979). Inhibitory, GABAergic nerve terminals decrease at sites of focal epilepsy. *Science, 205*, 211–214.

Ribak, C. E., Hunt, C. A., Bakay, R. A. E., and Oertel, W. H. (1986). A decrease in the number of GABAergic somata is associated with the preferential loss of GABAergic terminals at epileptic foci. *Brain Research*, *363*, 78–90.

Ribak, C. E., Joubran, C., and Bakay, R. A. E., (1987). A decrease in the number of GABAergic somata occurs in pre-seizing monkeys with alumina gel granuloma. *Epilepsy Research* (in press).

Ribak, C. E., and Khan, S. U. (1987). The effects of knife cuts of hippocampal pathways on epileptic activity in the seizure-sensitive gerbil. *Brain Research*, *418*, 146–151.

Roberts, E. (1986). Failure of GABAergic inhibition: A key to local and global seizures. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 319–341). New York: Raven Press.

Roberts, E. (1987). What do GABA neurons really do? They make possible variability generation in relation to demand. *Journal of Mind and Behavior*, *8*, 591–604.

Roberts, R. C. Kim, H. L., and Ribak, C. E. (1985). Increased numbers of neurons occur in the inferior colliculus of the young genetically epilepsy prone rat. *Developmental Brain Research*, *23*, 277–281.

Roberts, R. C., Ribak, C. E., and Oertel, W. H. (1985). Increased numbers of neurons occur in the inferior colliculus of an audiogenic model of genetic epilepsy. *Brain Research*, *361*, 324–338.

Schwartzkroin, P. A. (1986). Hippocampal slices in experimental and human epilepsy. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 991–1010). New York: Raven Press.

Seyfried, T. N., Glaser, G. H., Yu, R. K., and Palayoor, S. T. (1986). Inherited convulsive disorders in mice. In A. V. Delgado-Escueta, A. A. Ward, D. M. Woodbury, and R. J. Porter (Eds.), *Basic mechanisms of the epilepsies. Molecular and cellular approaches* (pp. 115–133). New York: Raven Press.

Sloper, J. J., Johnson, P., and Powell, T. P. S. (1980). Selective degeneration of interneurons in the motor cortex of infant monkeys following controlled hypoxia: A possible cause of epilepsy. *Brain Research*, *198*, 204–209.

Somogyi, P., Freund, T. F., and Cowey, A. (1982). The axo-axonic interneuron in the cerebral cortex of the rat, cat and monkey. *Neuroscience*, *7*, 2577–2609.